BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2007.03008.x

Effect of homeopathy on analgesic intake following knee ligament reconstruction: a phase III monocentre randomized placebo controlled study

A. Paris,[1,2] N. Gonnet,[1] C. Chaussard,[3] P. Belon,[4] F. Rocourt,[5] D. Saragaglia,[3] & J. L. Cracowski[1,2]

[1]Inserm, CIC003, CHU Grenoble, Grenoble F-38043, [2]Inserm ERI 17, University Grenoble 1, Faculté de Médecine, IFR1, Grenoble F-38042, [3]Department of Orthopaedic Surgery, CHU Grenoble, Grenoble F-38043, [4]Laboratoires BOIRON, St Foy-lès-Lyon F-69110 and [5]Department of Anaesthesia-reanimation, CHU Grenoble, Grenoble F-38043, France

Correspondence
Dr J. L. Cracowski, Inserm ERI 17, University Grenoble 1, Faculté de Médecine, IFR1, Grenoble F-38042, France.
E-mail: jlcracowski@chu-grenoble.fr

Keywords
analgesia, homeopathy, knee ligament reconstruction, pain

Received
25 April 2007

Accepted
4 June 2007

Published *OnlineEarly*
9 August 2007

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The efficacy of homeopathy is still under debate and a recent meta-analysis recommended further randomized double-blind clinical trials to identify any clinical situation in which homeopathy might be effective.

WHAT THIS STUDY ADDS

- The complex of homeopathy tested in this study (*Arnica montana* 5 CH, *Bryonia alba* 5 CH, *Hypericum perforatum* 5 CH and *Ruta graveolens* 3 DH) is not superior to placebo in reducing 24 h morphine consumption after knee ligament reconstruction.

AIMS

The efficacy of homeopathy is still under debate. The objective of this study was to assess the efficacy of homeopathic treatment (*Arnica montana* 5 CH, *Bryonia alba* 5 CH, *Hypericum perforatum* 5 CH and *Ruta graveolens* 3 DH) on cumulated morphine intake delivered by PCA over 24 h after knee ligament reconstruction.

METHODS

This was an add-on randomized controlled study with three parallel groups: a double-blind homeopathic or placebo arm and an open-label noninterventional control arm. Eligible patients were 18–60 years old candidates for surgery of the anterior cruciate ligament. Treatment was administered the evening before surgery and continued for 3 days. The primary end-point was cumulated morphine intake delivered by PCA during the first 24 h inferior or superior/equal to 10 mg day^{-1}.

RESULTS

One hundred and fifty-eight patients were randomized (66 in the placebo arm, 67 in the homeopathic arm and 25 in the noninterventional group). There was no difference between the treated and the placebo group for primary end-point (mean (95% CI) 48% (35.8, 56.3), and 56% (43.7, 68.3), required less than 10 mg day^{-1} of morphine in each group, respectively). The homeopathy treatment had no effect on morphine intake between 24 and 72 h or on the visual analogue pain scale, or on quality of life assessed by the SF-36 questionnaire. In addition, these parameters were not different in patients enrolled in the open-label noninterventional control arm.

CONCLUSIONS

The complex of homeopathy tested in this study was not superior to placebo in reducing 24 h morphine consumption after knee ligament reconstruction.

Introduction

Homeopathy, an approach to treatment introduced by Hahnemann, is widely used in daily medical practice. It is based on preparations of substances whose effect is intended to correspond to the clinical manifestations of the disease. Homeopathy is based on two principles: that the administration of the active element at higher concentrations causes the clinical signs of the disease and that the homeopathic treatment retains its biological activity after dilution, even if after successive dilutions the probability of the presence of any active molecule is very low. Although its use is widespread, its efficacy remains strongly debated. Several meta-analyses have tried to determine whether homeopathy is on the whole an effective therapeutic treatment [1–3]. The data have not concluded that homeopathy is not effective, but on the other hand, neither have they identified any clinical situation in which homeopathy is effective. In a meta-analysis performed in 1997 by Linde *et al.* [3], the results were not compatible with the hypothesis that the clinical effects of homeopathy are totally due to a placebo effect. All the same, there was no proof that homeopathy was effective for any single clinical condition. In 2000, Cucherat *et al.* [1] analyzed the results of all published and nonpublished randomized controlled clinical trials relative to the efficacy of a homeopathic treatment *vs.* placebo, up until June 1998. Primary endpoints had to be clinical endpoints and not biological markers. There was some suggestion for the efficacy of homeopathy. However, the level of evidence from the included trials was low and it was recommended that this result should be confirmed with higher quality studies. Linde further evaluated the impact of study quality on outcome [4]. He concluded that there was clear evidence that studies with better methodological quality tended to yield less positive results. In 2002, a new systematic review was performed by Ernst [2], exploiting electronic databases. No condition was found in which the response was better with homeopathy than with controls or no homoeopathic treatment. All these studies have stressed the need for further studies that comply with good clinical practice guidelines so as to identify under which conditions, if any, effectiveness might be demonstrated. Few studies are available on the evaluation of homeopathy as an analgesic for postsurgical pain. Moreover, the number of patients is usually small and the results debatable [5, 6]. Lokken *et al.* [5] conducted a randomized double-blind, placebo controlled cross-over trial to examine whether homeopathy had any effect on pain and other inflammatory events following oral surgery. Twenty-four patients were included and started the treatment 3 h after surgery. The pain intensity was about the same in the two treatment arms and 13 patients preferred the postoperative 'treatment' with placebo. In another study, 130 patients undergoing saphenous stripping were included in a randomized, prospective multicentre double-blind placebo controlled trial to determine whether homeopathic *Arnica* could reduce postoperative haematomas [6]. Nurses administered the treatments the night before and immediately after surgery and haematomas were clinically evaluated at 6 days after surgery. No statistical difference was found between the *Arnica* and placebo groups. Recently, it has been suggested that homeopathic treatment with *Arnica* decreases knee swelling and pain following cruciate ligament reconstruction [7]. However, no data are available on the consumption of analgesics by these patients.

Our objective in the present study was to evaluate the efficacy of an add-on homeopathic treatment *vs.* placebo on analgesic consumption in knee ligament reconstruction. The primary end-point was the consumption of morphine over the first 24 h following surgery. As a secondary objective, a control group without intervention was included to allow the placebo effect to be assessed.

Methods

Patients

The protocol and the informed consent form were approved by the ethics committee 'Comité Consultatif de Protection des Personnes de Grenoble', France, on the 12 November 2003. Subjects were enrolled between the 28 November 2003 and 3 April 2006 during a consultation with the anaesthetist at the Grenoble University Hospital, France. Inclusion criteria were: male or female aged from 18 to 60 years and a candidate for surgery of the anterior cruciate ligament by the Kenneth-Jones (KJ) or the doubled semitendinosus and gracilis tendons (DGST) technique. Exclusion criteria were current use of immunosuppressive drugs and/or corticosteroid treatment.

Objective and end-points

The objective of the study was to assess the efficacy of homeopathic treatment on cumulated morphine intake delivered by patient controlled analgesia (PCA) 24 h after knee ligament reconstruction. The primary end-point was the cumulated consumption of morphine delivered by PCA during the first 24 h following surgery. Evaluation of this primary end-point was qualitative: consumption of <10 mg of morphine or >10 mg over the first 24 h. Secondary objectives were: the efficacy of homeopathic treatment on cumulated morphine oral intake between 24 and 72 h after knee ligament reconstruction, the efficacy of homeopathic treatment on pain perception during 72 h after surgery, the evaluation of the quality of life 1 month after surgery and the placebo effect linked to the intake of the homeopathic preparation. The secondary end-points were the number of boluses of morphine between 0 and 24 h after surgery; cumulated consumption of morphine between 0 and 24 h and between 24 and 72 h after

surgery, pain evaluation using a visual analogue scale (VAS) and quality of life as assessed by the SF-36 questionnaire (Short-form-36).

Sample size

According to previous records in the same hospital setting the number of subjects expected to consume less than 10 mg of morphine was 55%. As our objective was to detect a 20% improvement of this value with homeopathy, and with $\alpha = 0.05$ and a power $(1-\beta)$ of 80%, then 68 subjects per group were required. We decided to include 70 subjects per group (homeopathy and placebo groups). We initially planned to include 70 patients in the third no-intervention (neither homeopathy nor placebo) group. However, due to delays in enrolment, this group was stopped on 28 January 2005, halfway through the enrolment period, to enable us to fulfil the primary objective, with the same budget. As a consequence, all data concerning the nonintervention group are given as descriptive statistics and no test was performed.

Homeopathic treatment

This was a complex of four active elements incorporated in the same granule. The four elements were *Arnica montana* 5 CH, *Bryonia alba* 5 CH, *Hypericum perforatum* 5 CH and *Ruta graveolens* 3 DH. The complex was defined by a physician specialized in homeopathy after clinical examinations between day 0 and day 4 of patients undergoing knee ligament reconstruction surgery. Patients were required to take 5 granules each time. Patients were not allowed to eat between 30 min before and 1 h after taking the treatment. They were not allowed to smoke, to drink tea or coffee, or to use any compound with mint between 0.5 h before and after treatment. Homeopathic treatment was add-on to the other analgesic treatments. The postoperative management of pain was standardized: immediately after surgery an injection of ropivacaine (0.75% 20 ml) was given crurally to obtain a contraction of the quadriceps through the neurostimulator. This was associated with nonsteroidal anti-inflammatory medication (NSAI; ketoprofen 50 mg 24 h^{-1} in four doses) and with a perfusion of acetaminophen at a dose of 1 g 6 h^{-1}. A protocol of PCA was performed during the first 24 h. Every bolus corresponded to a dose of 1 mg of morphine for patients under 80 kg and of 1.5 mg for patients over 80 kg. The minimum period between the two boluses was 15 min. At 24 h, there was oral dosing: ketoprofen 150 mg two tablets 24 h^{-1}, acetaminophen 500 mg 6 tablets 24 h^{-1} and morphine sulphate 20 mg 24 h^{-1} if the VAS was >3.

Design

This was an add-on randomized controlled study with three parallel groups: a double-blind homeopathic or placebo arm and an open-label noninterventional control arm. After verification of inclusion and exclusion criteria and clinical examination by the anaesthetist, patients signed the informed consent form, were asked their opinion about homeopathy and completed the SF-36 quality of life questionnaire. They were randomized a few days before surgery. Stratification was based on the surgical technique and the surgeon (Dr X, Dr Y or other). The size of the blocks was variable and generated by an independent operator. The treatment number was allocated after a protected connection on intranet system of randomization. The blinding code was kept at the pharmacy in closed envelopes. Study treatment was started the evening before surgery and continued for 3 days. General anaesthesia was induced using a standardized protocol with sufentanil or propofol maintained with sufentanil and sevorane. Sufentanil and bupivacaine were used for regional anaesthesia. Evaluation of pain and the consumption of morphine were recorded during the study treatment period. About 1 month later, the patients were sent the SF-36 questionnaire again and questions about their views on homeopathy, with a prestamped envelope for return.

Statistical analysis

Quantitative data were described by mean and 95% confidence interval (CI). Qualitative data were described by size, percentage and 95% CI. For the primary end-point, a χ^2 test was performed. For all analyses, a *P* value was given with an α risk of 5%. A *P* value less than 0.05 was considered as significant. All analyses were performed with intention to treat, except for the primary end-point, which was presented in a per protocol analysis as a secondary objective.

Results

Study population

One hundred and ninety-nine patients were eligible for the study, 180 were enrolled and 158 randomized. The distribution into each group and the reasons for any discontinuation are shown in Figure 1. The characteristics of the population are described in Table 1. Patient opinions about homeopathy are summarized in Table 2. The distribution of patients into each treatment arm was homogenous due to the stratification based on the surgeon and the surgical technique. There was no reason to unblind the treatments during the study and all the envelopes were kept closed until the end of the statistical analysis.

Primary end-point

There was no statistical difference between the two treatment groups in terms of morphine intake at 24 h (Figure 2): relative to intention to treat analysis, mean (95% CI) 48% (35.8, 60.2) of patients in the group treated with homeopathy and 56% (43.7, 68.3) of patients receiving placebo ($P = 0.42$) consumed less than 10 mg of morphine day^{-1} during the first 24 h. The difference between the two

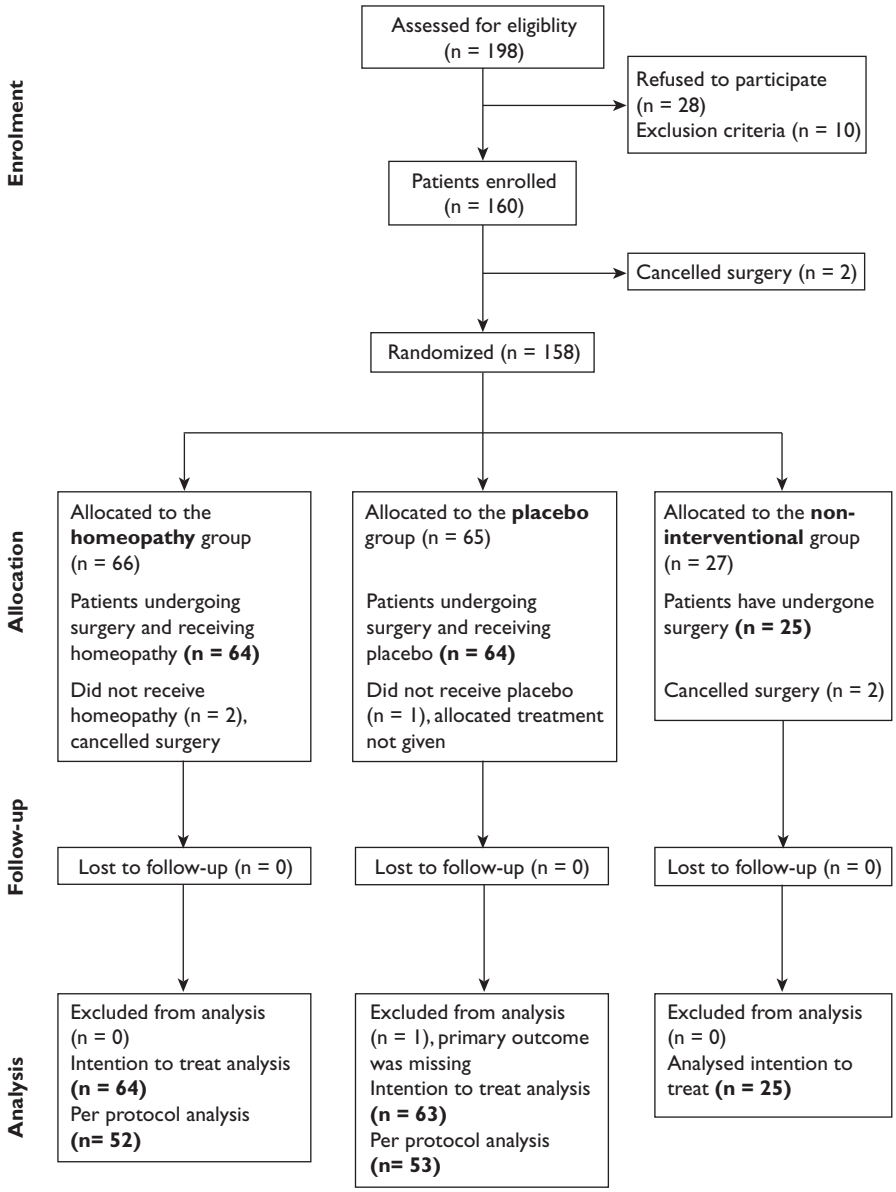

Figure 1

Study flow chart. All patients were included in the intention to treat analysis except one patient whose primary outcome was missing. All patients who took exactly the number of homeopathic globules prescribed were included in the per protocol analysis

groups (homeopathy – placebo) was –8 (–16.8, 0.8). According to per protocol analysis, 45% (31.5, 58.5) of patients in the group treated with homeopathy and 55% (41.6, 68.4) of patients receiving placebo ($P = 0.28$) consumed less than 10 mg of morphine day^{-1} during the first 24 h. The difference between the two groups (homeopathy – placebo) was –10 (–20.0, 0.0).

Secondary end-points

There was no difference in the consumption of morphine between the two intervention study groups during the first 24 h (15.1 mg (11.2, 19.0), 13 mg (9.5, 16.5) and 12.8 mg (6.5, 19.1), respectively, in the group treated with homeopathy, in the group receiving placebo and in the non-treated group, $P = 0.08$. Difference between the two treated groups (homeopathy-placebo) was 2.14 (–3.2–7.4). Morphine consumption during the following 48 hours were 15.7 mg (10.4, 21.0), 19.4 mg (13.3, 25.5) and 18.7 mg (7.5, 29.9), respectively, in the group treated with homeopathy, in the group receiving placebo and in the non-treated group, $P = 0.08$. The difference between the two treated groups (homeopathy – placebo) was –3.68 (–11.7, 4.4) (Figure 3). Likewise, for pain assessed by VAS, there was no significant difference between the groups. For the

Table 1

Study population. Data are given as mean (95% confidence interval) or percentage

	Homeopathy $n = 64$	Placebo $n = 63$	Open-label non interventional arm $n = 25$
Age (years)	31 (13.4, 48.6)	32 (12.4, 51.6)	31 (11.4, 50.6)
Sex (% of women)	39 (27.1, 50.9)	29 (17.8, 40.2)	44 (12.2, 37.8)
Smoking (%)	36 (24.2, 47.8)	33 (21.4, 44.6)	48 (33.2, 62.8)
Educational level %			
Secondary school	3 (–1.2, 7.2)	11 (3.3, 18.7)	16 (5.2, 26.9)
High school	42 (29.9, 54.1)	38 (26.0, 50.0)	48 (33.2, 62.8)
Higher education	55 (42.8, 67.2)	51 (38.7, 63.3)	36 (21.8, 50.2)
BMI (kg m^{-2})	24 (18.1, 29.9)	24 (18.1, 29.9)	23 (17.1, 28.9)
DAP (mm Hg)	70 (50.4, 89.6)	69 (49.4, 88.6)	68 (42.5, 91.5)
Cardiac frequency (beats min^{-1})	71 (43.6, 98.4)	66 (46.4, 85.6)	68 (42.5, 93.5)
Time between inclusion and surgery (days)	22 (–11.3, 55.3)	19 (–18.2, 56.2)	17 (–0.63, 4.6)
Type of surgery			
DGST	64 (52.5, 75.8)	65 (53.2, 76.8)	68 (54.2, 81.8)
KJ	36 (24.2, 47.8)	35 (23.2, 46.8)	32 (18.2, 45.8)
General anaesthesia (%)	30 (18.8, 41.2)	45 (32.7, 57.3)	60 (45.5, 74.5)
Crural block (%)	88 (80.0, 96.0)	89 (81.3, 96.7)	76 (63.9, 88.1)
Surgeon (%)			
Dr X	25 (14.4, 35.6)	21 (10.9, 31.1)	28 (14.7, 41.3)
Dr Y	44 (31.8, 56.2)	45 (32.7, 57.3)	40 (25.5, 54.5)
Others	31 (19.7, 42.3)	34 (22.3, 45.7)	32 (18.2, 45.8)
Adverse events (%)	12.5 (4.4, 20.6)	8 (1.3, 14.7)	16 (5.2, 26.8)
Severe adverse events (%)	0	0	0

BMI body mass index; DAP diastolic arterial pressure; DGST: doubled semitendinosus and gracilis tendons; KJ: Kenneth Jones; PCA: patient controlled anaesthesia.

Table 2

Opinions about homeopathy at enrolment. Data are given as percentages

	Homeopathy $n = 64$	Placebo $n = 63$	Open-label noninterventional arm $n = 25$
Do you think that homeopathic therapy is efficient?	62/16/22	73/19/8	64/20/16
Yes/No/Do not know (%)			
Do you think that homeopathic therapy is efficient in knee ligament reconstruction?	47/12/47	48/11/41	48/8/44
Yes/No/Do not know (%)			
Do you think you will have pain relief with homeopathy therapy?	33/23/44	38/27/35	24/28/48
Yes/No/Do not know (%)			
Have you already used homeopathic therapy?	72	84	72
Yes (%)			
Have you already used homeopathic therapy for any pain?	45	52	44
Yes (%)			

placebo group the VAS score was 1.2 (–2.0, 4.4) at 0 h, 1.8 (–2.0, 5.6) at 4 h, 2.2 (–1.6–6.0) at 24 h and 0.8 (–1.8, 3.4) at 72 h and for the group treated with homeopathy: 1.5 (–2.4, 5.4) at 0 h, 1.2 (–1.7, 4.06) at 4 h, 2.0 (–1.7, 5.7) at 24 h and 1.2 (–1.8, 4.2) at 72 h (data not shown). The difference in VAS for pain between the two treated groups (homeopathy – placebo) was, 0.3 (–0.4, 0.9), –0.6 (–1.2, 0.0), –0.2 (–0.9, 0.5) and 0.3 (–0.3, 0.9) at 0, 4, 24 and 72 h, respectively. The quality of life assessed by the SF-36 questionnaire showed a difference between day 0 and month 1 ($P < 0.001$), but there was no difference at 1 month between the two intervention groups. The difference (homeopathy – placebo) was 1.1 (–3.0, 5.2) at day 0 and –2.6 (–1.7, 6.9) at 1 month. At day 0, the score of the SF-36 questionnaire was 90.8 (87.5, 94.1), 89.7 (87.2, 92.2), and 87.5 (82.2, 92.8), respectively, in the group treated with homeopathy, in the groups receiving placebo and in the nontreated group, $P = 0.16$. At 1 month, it was 80.7 (77.8, 83.6), 83.3 (80.4, 86.2), and 77.6 (72.9, 82.3), respectively, in the group treated with homeopathy, in the groups receiving placebo and in the nontreated group, $P = 0.24$ (Figure 4). There was also no difference in the score evaluating physical activity calculated from the SF-36 questionnaire after surgery. However, there was a significant difference in

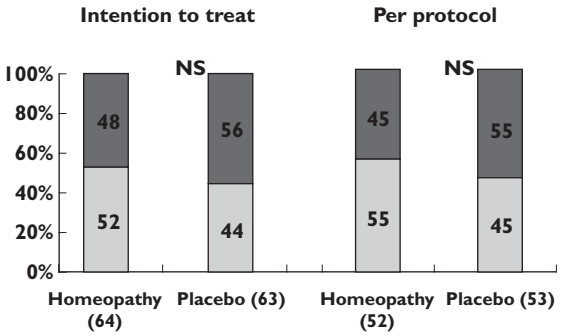

Figure 2

Morphine intake at 24 h. NS: Not significant. <10 mg/d, (■); >= 10mg/d, (□)

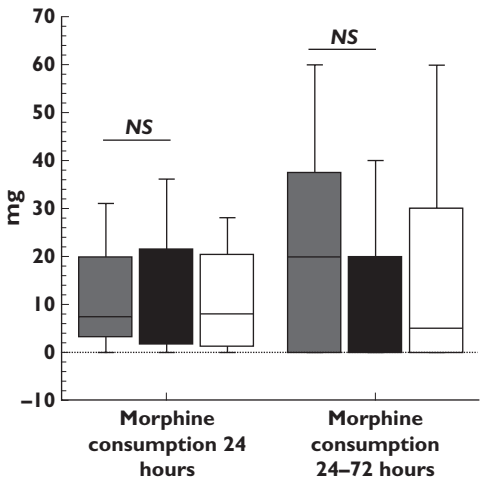

Figure 3

Consumption of morphine in the three study groups during the first 24 h and the following 48 h. Data for the nonintervention group are given as descriptive due to the small size. NS: not significant. Placebo, (■); Homeopathy, (■); Non-treated control arm, (□)

the psychological score ($P < 0.001$) (data not shown). The logistic regression allowed us to identify the factors influencing morphine intake over the first 24 h: smoking ($P = 0.018$), age ($P = 0.005$) and surgeon ($P = 0.003$).

Patient opinions about homeopathic treatment

In subjects enrolled in the placebo or homeopathic groups ($n = 127$), there was a difference in the response to the question 'do you think that homeopathy is effective?': 67% (57.1, 76.9), *vs.* 78% (69.0, 87.0) for 'yes', 18% (1.9, 34.0) *vs.* 17% (–0.9, 34.9) for 'no' and 15% (–1.1, 31.1) *vs.* 5% (–12.4, 22.4) for 'do not know' ($P < 0.0001$), before and after treatment, respectively. Similarly, there was a difference in replies to the question: 'do you think that homeopathy is useful for knee ligament reconstruction?' before and after surgery: 47% (34.4, 59.6), *vs.* 61% (49.1, 72.9), for 'yes', 11%

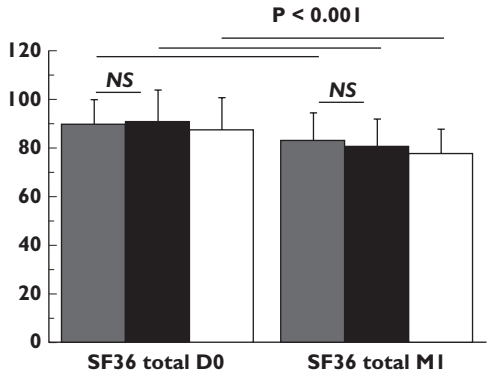

Figure 4

Quality of life assessed by the SF-36 questionnaire. Data for the nonintervention group are given as descriptive due to the small size. SF: Short-form. NS: Not significant. Placebo, (■); Homeopathy, (■); Non-treated control arm, (□)

(–4.8, 26.8) *vs.* 33% (17.4, 48,6) for 'no' and 42% (28.6, 55,4) *vs.* 6% (–13.0, 25.0) for 'do not know' ($P < 0.0001$). To the question 'Do you think your pain decreased thanks to homeopathy?' 49% (35.3, 62.7), of the patients answered 'yes', 41% (26.1, 55.9), 'no' and 10% (–7.7, 27.7) 'do not know'. Before surgery, 77% (68.7, 85.3), of the patients answered that they had previously taken homeopathic treatment and after surgery 85% (77.6, 92.4), declared that they would use homeopathy in the future ($P < 0.01$).

No adverse event was reported during the study.

Discussion

The homeopathic treatment tested in this study was no better than placebo for postoperative pain management after knee ligament reconstruction. Furthermore, this treatment seemed to have no placebo effect in these conditions. However, inclusion in a trial that evaluates homeopathy leads to an improvement in the patient's opinion about the treatment irrespective of the results.

The results of this study raise several issues that should be addressed. First, relative to the primary objective of the study, the pain following this type of surgery may have been less than anticipated. In fact, 88% of the patients in the homeopathic group and 89% of the patients in the placebo group received a crural block during surgery, i.e. they received an injection of ropivacaine (a local anaesthetic) in the crural nerve just after surgery. However, the percentage of patients consuming 10 mg of morphine or more per day is close to that of previously available data, used for calculation of the number of subjects needed. Another issue is the small size of the open-label nonintervential control arm. While this does not change the primary objective, we are unable to draw a conclusion concerning any placebo effect. As explained previously, due to

delays in patient inclusion we had to terminate enrolment of patients in this group for budgetary reasons.

We performed a research in PubMed about 'pain' and '*Arnica*' restricted to 'clinical trials', 'randomized controlled trial' and 'meta analysis' in 'humans'. We found 12 studies in different medical situations. The results are different according to the studies (five with positive results and seven with negative results): the positive results were obtained after carpal-tunnel release surgery after 2 weeks of treatment [8], in osteoarthritis of the knee after 6 weeks of treatment with a gel containing *Arnica* [9], on pain due to muscle soreness in an analysis of pooled results of two double-blind studies in marathon runners [10], in healthy volunteers in association with hydroxyethyl salicylate [11], and in post-tonsillectomy [12]. The negative results were observed in the following situations: prevention of pain after removal of wisdom teeth [13], in the first of the two studies in marathon runners [14] and in another study after long-distance running [15], after total hysterectomy [16], after surgery for carpal tunnel syndrome [17] and varicose vein surgery [18] and recently, in cruciate ligament reconstruction [7]. The results of this trial which is similar to ours merit discussion [7]. The authors performed three double-blind randomized trials on the administration of *Arnica montana* at a homeopathic dilution (30 times) in knee surgery. One of the surgical procedures was cruciate ligament reconstruction, similar to our study. They evaluated the relative change in knee circumference at day 2 after surgery (ratio of circumference on day 2 after surgery to baseline circumference). The drug (3×5 globules) was given 2 h before surgery then postoperatively at 3 h intervals after the recovery phase and from the second postoperative day three times a day until day 11. Seventy-one patients were included and 57 were analyzed. There was a minor significant difference between placebo and homeopathic therapy for the change in knee circumference ($P = 0.019$) and pain at day 1 ($P = 0.05$). However they failed to demonstrate any difference at day 2. Similarly no difference was observed following knee arthroscopy and artificial knee joint implantation. While the authors recommend the use of *Arnica* given its low cost, our data, based on a more consistent end point (24 h intravenous morphine intake) and on a larger number of subjects do not support this data.

The choice of the composition of the homeopathic therapy used in our study should be discussed. In fact, the different elements were chosen a *priori* after an initial appraisal of the surgery. We chose not to consider a personalized prescription, but to test a combination of homeopathic treatments.

Indeed, one of the greatest difficulties when trying to perform double-blind clinical trials *vs.* placebo to assess homeopathy is due to the usual mode of prescription of this therapy: the treatment is usually very patient specific. For a given diagnosis, homeopathy consultants use a large variety of treatments and the same treatment may be prescribed for several very different pathologies. This leads to three different options for the conduct of double-blind placebo-controlled clinical trials with personalization of the treatment: 1) to put several substances at the practitioners disposal available both in veritable form and in placebo form; 2) to preselect patients so as to obtain a population who will receive the same homeopathic therapy for a specific indication; or 3) to prescribe in accordance to the practices of homeopathy therapy, i.e. the practitioner prescribes what he thinks to be best for each patient, the prescription is sent to a randomization centre, the drugs are manufactured in active or placebo form and given to the patients in a double-blind fashion. This third option is the most complex to apply. Numerous clinical trials have been realized using one or other of these methods, although the first method is probably most common. One example is a clinical trial in rheumatoid polyarthritis [19]. In a double-blind protocol 46 patients received one or more active substances or the corresponding placebo over a period of 6 months. There was a significant improvement in pain relief for patients receiving the homeopathic therapy but no effect on inflammation.

Another issue about homeopathy is that if it is effective, this is due to of a potential placebo effect. Yet in our study, this tendency was not observed, although because of the small size of the nonintervention group, we cannot draw a definitive conclusion. Amongst the several meta-analyses that have been performed of trials to assess the efficacy of homeopathic treatments, one demonstrating that homeopathic therapy does not have a placebo effect should be noted [3]. The authors examined the results of 89 clinical trials and concluded that the results of their meta-analysis were not compatible with the hypothesis that the clinical effects of homeopathy are completely due to a placebo effect. They concluded that if homeopathy is effective, it is due to the substances consumed and not simply due to the fact that the patient has taken medication.

To conclude, the complex of homeopathy used in this study (*Arnica montana* 5 CH, *Bryonia alba* 5 CH, *Hypericum perforatum* 5 CH and *Ruta graveolens* 3 DH) is not superior to placebo in reducing 24 h morphine consumption after knee ligament reconstruction.

We thank Alison Foote (Inserm CIC003, CHU Grenoble) for correcting the manuscript.

Conflicts of interest: Dr Belon is the head of the clinical research department of Laboratoires Boiron. The Laboratoires Boiron financially supported the study. None of the other investigators had any conflict of interest.

REFERENCES

1 Cucherat M, Haugh MC, Gooch M, Boissel JP. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical

trials. HMRAG Homeopathic Medicines Research Advisory Group. Eur J Clin Pharmacol 2000; 56: 27–33.

2 Ernst E. A systematic review of systematic reviews of homeopathy. Br J Clin Pharmacol 2002; 54: 577–82.

3 Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997; 350: 834–43.

4 Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo-controlled trials of homeopathy. J Clin Epidemiol 1999; 52: 631–6.

5 Lokken P, Straumsheim PA, Tveiten D, Skjelbred P, Borchgrevink CF. Effect of homoeopathy on pain and other events after acute trauma: placebo controlled trial with bilateral oral surgery. BMJ 1995; 310: 1439–42.

6 Ramelet AA, Buchheim G, Lorenz P, Imfeld M. Homeopathic *Arnica* in postoperative haematomas: a double-blind study. Dermatology 2000; 201: 347–8.

7 Brinkhaus B, Wilkens JM, Ludtke R, Hunger J, Witt CM, Willich SN. Homeopathic arnica therapy in patients receiving knee surgery: results of three randomised double-blind trials. Complement Ther Med 2006; 14: 237–46.

8 Jeffrey SL, Belcher HJ. Use of Arnica to relieve pain after carpal-tunnel release surgery. Altern Ther Health Med 2002; 8: 66–8.

9 Knuesel O, Weber M, Suter A. *Arnica montana* gel in osteoarthritis of the knee: an open, multicenter clinical trial. Adv Ther 2002; 19: 209–18.

10 Tveiten D, Bruset S. Effect of *Arnica* D30 in marathon runners. Pooled results from two double-blind placebo controlled studies. Homeopathy 2003; 92: 187–9.

11 Kucera M, Horacek O, Kalal J, Kolar P, Korbelar P, Polesna Z. Synergetic analgesic effect of the combination of *Arnica* and hydroxyethyl salicylate in ethanolic solution following cutaneous application by transcutaneous electrostimulation. Arzneimittelforschung 2003; 53: 850–6.

12 Robertson A, Suryanarayanan R, Banerjee A. Homeopathic *Arnica montana* for post-tonsillectomy analgesia: a randomised placebo control trial. Homeopathy 2007; 96: 17–21.

13 Kaziro GS. Metronidazole (Flagyl) and *Arnica montana* in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. Br J Oral Maxillofac Surg 1984; 22: 42–9.

14 Tveiten D, Bruseth S, Borchgrevink CF, Lohne K. [Effect of *Arnica* D 30 during hard physical exertion. A double-blind randomized trial during the Oslo Marathon 1990]. Tidsskr Nor Laegeforen 1991; 111: 3630–1.

15 Vickers AJ, Fisher P, Smith C, Wyllie SE, Rees R. Homeopathic *Arnica* 30x is ineffective for muscle soreness after long-distance running: a randomized, double-blind, placebo-controlled trial. Clin J Pain 1998; 14: 227–31.

16 Hart O, Mullee MA, Lewith G, Miller J. Double-blind, placebo-controlled, randomized clinical trial of homoeopathic *Arnica* C30 for pain and infection after total abdominal hysterectomy. J R Soc Med 1997; 90: 73–8.

17 Stevinson C, Devaraj VS, Fountain-Barber A, Hawkins S, Ernst E. Homeopathic *Arnica* for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. J R Soc Med 2003; 96: 60–5.

18 Wolf M, Tamaschke C, Mayer W, Heger M. [Efficacy of *Arnica* in varicose vein surgery: results of a randomized, double-blind, placebo-controlled pilot study]. Forsch Komplementarmed Klass Naturheilkd 2003; 10: 242–7.

19 Gibson RG, Gibson SL, MacNeill AD, Buchanan WW. Homoeopathic therapy in rheumatoid arthritis: evaluation by double-blind clinical therapeutic trial. Br J Clin Pharmacol 1980; 9: 453–9.